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Letter to the Editor

A Danish hospital outbreak of SARS-CoV-2. Combining whole-genome sequencing with epidemiological links offers surprising new information

Sir,

In relation to a recent paper describing transmission of SARS-CoV-2 among healthcare workers and patients in a teaching hospital in the Netherlands confirmed by whole-genome sequencing, we are sharing our experiences with a large hospital outbreak of SARS-CoV-2 [1]. The outbreak took place during the first wave of the pandemic at Nordsjællands Hospital (NOH), a 600-bed hospital situated north of Copenhagen, and comprised both patients and staff of various professions.

We first suspected a SARS-CoV-2 outbreak at NOH on May 21st, 2020, at ward A (a department of surgery). Accordingly, the ward immediately closed to new admissions, and screening of all patients and employees at the ward, as well as close contacts to all persons testing positive for SARS-CoV-2, was initiated. Isolation precautions were routinely initiated for both COVID-19-positive persons and close contacts according to national guidelines (SST.dk).

On May 23rd, we learned that the outbreak involved at least 10 patients and an unknown number of employees, but we also suspected spread to other departments of the hospital. After weeks of investigating epidemiological links throughout the hospital, we estimated that the outbreak involved in total 42 persons, and all had positive SARS-CoV-2 tests dated May 11th to June 6th, 2020. The outbreak comprised 15 patients from ward A, 21 physicians, nurses, nurse assistants, cleaners, and pharmacists employed in several wards working at two departments, one surgical and one medical. Furthermore, six employees from an administrative department had been infected through a meeting of 2 h duration with employees from ward A—the circumstances suggesting a superspreader event. Whole-genome sequencing (WGS) was done according to Michaelsen *et al.* and SARS-CoV-2 lineage assignment as described by O'Toole *et al.* [2,3]. Of the 42 outbreak isolates, 25 (60%) were available for WGS. All 25 isolates belonged to SARS-CoV-2 B.1.179, a lineage derived from B.1.

Taking advantage of our WGS database of isolates from NOH and its coverage area, we learned that in total 90 isolates of lineage B.1.179 had been identified in 2020, all between April 20th and August 18th (Figure 1). SARS-CoV-2 B.1.179 being a fairly rare clade leads to the assumption that all cases within the four-month timeframe probably were part of the same outbreak. Surprisingly, 40% of outbreak strains were sent by GPs or test sites, all between May 8th and August 18th, indicating that a considerable part of the outbreak may have taken place in the communities surrounding the hospital. The WGS data, however, indicate that the outbreak started as a nosocomial outbreak involving at least three different departments and then spread to the community, likely primarily through family relations.

Our infection prevention team was aware of just 28% of cases presented in Figure 1; thus, the vast majority of outbreak cases were unrecognized and the outbreak was indeed much larger than recognized using only epidemiological links. These data serve as a reminder to include strains from non-hospitalized patients when selecting strains for WGS. Epidemiological links tend to be less obvious when crossing sectors, which usually is what patients (and staff) do in real life.

Curious to have a look at the B.1.179 lineage in an international perspective we accessed <https://cov-lineages.org/lineage.html?lineage=B.1.179> [3]. In total 230 B.1.179 have been reported and the vast majority came from Denmark (88%). United Kingdom reported 5%, USA 3%, Mexico 1%, and Philippines 1% of the 215 B.1.179 lineage strains. Thus, this clade seems to be predominately Danish, present for just six months from March 9th to August 17th, 2020. The Pangolin overview is based on the SARS-CoV-2 genomes uploaded to GISAID from different countries. The uneven sequencing effort of each country would create a bias, as some countries sequence more genomes per inhabitant.

What we initially believed to be a nosocomial outbreak in a local hospital spreading to the community was in fact a six-month lasting national outbreak, lasting from March 9th to August 17th, 2020. The epidemiological links led us to believe that the outbreak started in May, but WGS (Figure 1) revealed that the probable index case was diagnosed at mid-April in ward B at the same surgical department. Moreover, looking at the international data the first known Danish isolate was found as early as March 9th (though not from the coverage area of NOH).

The picture we try to draw of an ongoing SARS-CoV-2 outbreak, or any outbreak for that matter, is bound to be

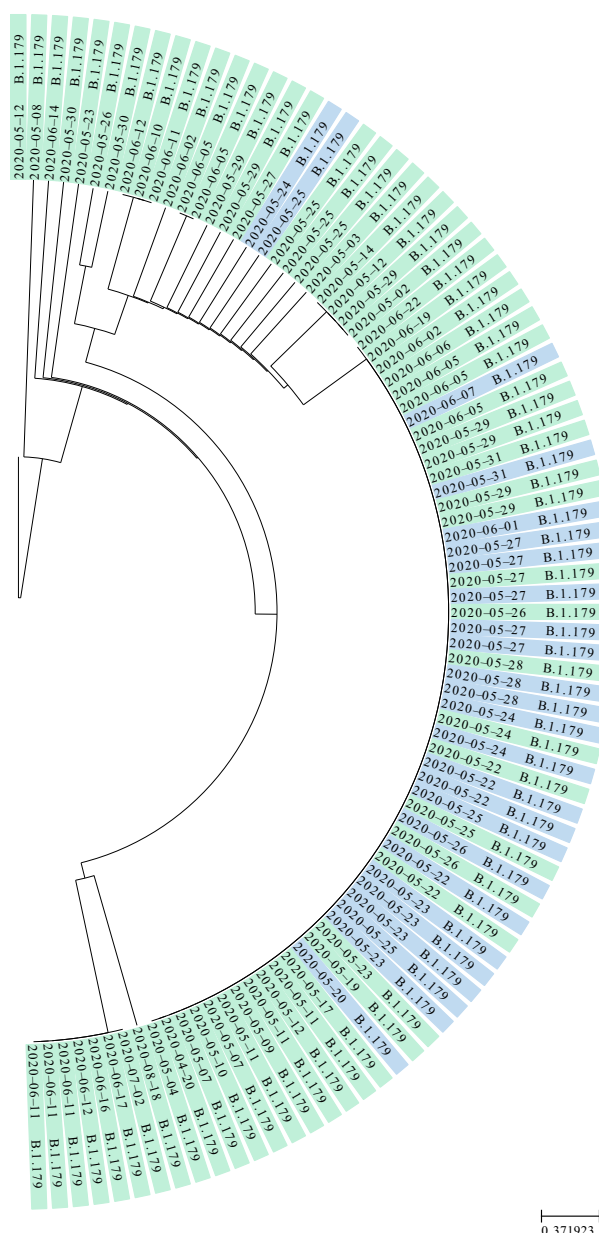


Figure 1. Phylogenetic whole-genome sequencing (WGS) single-nucleotide polymorphism-based tree comprising 90 SARS-CoV-2 B.1.179 lineage from the coverage area of Nordsjællands Hospital, Denmark, 2020. The green markings indicate outbreak strains recognized only by WGS whereas the blue markings indicate strains also recognized as outbreak strains through epidemiological links.

incomplete for a number of reasons; however, we find that combining WGS with epidemiological links proved helpful in

getting a fuller picture of the outbreak. WGS is an excellent tool, but the value of the data produced depends on whether WGS is performed in real time or *post festum*. In Denmark most departments of clinical microbiology therefore have begun performing WGS once a week in 2021, sending the sequences for national surveillance.

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Conflict of interest statement

None declared.

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